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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 01/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/750,620	WU ET AL.	
	Examiner	Art Unit	
	Fereydoun G. Sajjadi	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *12-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the papers filed December 2, 2005. Applicant's response to restriction requirement of November 2, 2005 has been entered. No claims were amended or withdrawn. Currently, claims 1-17 are pending in the application.

Election/Restrictions

Following the oral communication of November 21, 2005 with applicant's representative (Shelly M. Fujikawa), the species election requirement indicated in the restriction requirement of November 2, 2005 was withdrawn by the examiner and is hereby acknowledged for the record. Applicant's representative should note that claim 14 was not missing in the restriction requirement of November 2, 2005 and was indicated as a linking claim on page 3, third paragraph of the action. Claim 14 links inventions III and IV.

Applicant's election of Group I (claims 1-11), drawn to a recombinant plasmid AAV vector, comprising an HO-1 gene; a cell strain containing said vector; an AAV virus produced from said vector; and a process of producing recombinant AAV virus containing the HO-1 gene by transfecting a host cell with said vector or AAV virus, and a method of mediating HO-1 gene expression, comprising administering an effective amount of a recombinant AAV vector, is acknowledged. Claims 12-17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Because Applicant did not specifically traverse the requirement for election, the election requirement is maintained and hereby made final.

Claim Objections – Duplicate Claims

Applicant is advised that should claim 3 be found allowable, claim 4 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. Similarly, should claim 5 be found allowable, claims 6 and 7 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112-Biological Deposit

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification is not enabling without either complete evidence that the plasmid pSNAV1/HO and the recombinant virus HSV1-rc, recited in the claims are known and **readily available to the public** or complete evidence of the deposit of the biological material. Because the biological material is essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification or otherwise readily available to the public. If the biological material is not so obtainable or available, the requirements of 35 USC §112 may be satisfied by a deposit of the biological materials. The specification does not disclose a repeatable process to obtain the biological materials and it is not apparent if the biological materials are readily available to the public. The specification refers to the plasmid at various places, but does not state that all restrictions on the deposits will be irrevocably removed on issuance of a patent and that the deposit will be replaced if viable samples cannot be dispensed by the depository is require. Further, the description regarding the construction of pSNAV1/HO-1 on page 9 and the description of HSV1-rc on p. 10 of the instant specification lack sufficient detail to allow its reproduction without undue experimentation. In the absence of evidence showing that the plasmid is publicly available (i.e., deposited in compliance with 37 CFR 1.801-1.809) or can be constructed or isolated without undue experimentation, claims 1-10 are not supported by an enabling disclosure.

A suitable deposit for patent purposes would overcome this ground of rejection. Deposits should be made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicants, assignees or a statement by an attorney of record over his or her signature and registration number stating that the deposits have been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced

if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State. Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As a possible means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

As a possible means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit. The Examiner notes that, if Applicant argues that the strains are well known and readily available to the public, the claims drawn in part to this plasmid will only remain enforceable while the plasmid remains readily available to the public. If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR §§1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;

(d) a test of the viability o the biological material at the time of deposit will be made (see 37 CR §1.807); and

(e) the deposit will be replaced if it should ever become unviable.

Applicant's attention is directed to MPEP §2400 in general, and specifically to §2144.05, as well as to 37 CFR §1.809(d), wherein it is set forth that "the specification shall contain the accession number for the deposit, the date of the deposit, the name and address of the depository, and a description of the deposited material sufficient to specifically identify it and to permit examination." The specification should be amended to include this information, however, Applicant is cautioned to avoid the entry of new matter into the specification by adding any other information.

Claim Rejections - 35 USC § 112-Indefinite

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 11 is rejected under 35 USC § 112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as his invention.

Claim 11 is unclear. The claim recites a method of mediating expression of the HO-1 gene, wherein the method comprises administering an effective amount of a recombinant adeno-associated viral vector. When given its broadest reasonable interpretation, it is not clear whether said mediating entails an increase or decrease or other alteration of the expression of the HO-1 gene and it is not clear whether such administering is to a patient, or a cell or tissue *in vitro*. Therefore, the metes and bounds for mediating and administering are not defined.

Claim Rejections - 35 USC § 112-Lack of Enablement

Claims 9 and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification is not enabling for a method of mediating expression of the HO-1 gene, wherein the method comprises administering an effective amount of a recombinant adeno-associated viral vector (claim 11) or a process for the production of the recombinant rAAV/HO-1 virus comprising transforming a host cell with pSNAV1/HO-1 and HSV1-rc (claim 9).

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404:

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

MPEP § 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection."

The Nature Of The Invention And Breadth Of Claims

Claim 9 is drawn to a process for the production of the recombinant rAAV/HO-1 virus comprising transforming a host cell with pSNAV1/HO-1 and HSV1-rc. Claim 11 is drawn to a method of mediating expression of the HO-1 gene, wherein the method comprises administering an effective amount of a recombinant adeno-associated viral vector. Given its broadest reasonable interpretation, claim 9 encompasses recombinant AAV virus production in a host cell *in vitro* or *in vivo* in any and all cell types that may serve as hosts to pSNAV1-HO-1 and HSV1-rc. Claim 11 encompasses any and all effects on alterations of HO-1 gene expression, under any and all conditions that may be described as mediating, that can include gene therapy. Claim 11 also encompasses the administration of any recombinant AAV virus that can mediate expression of an HO-1 gene, including an AAV virus, not bearing the HO-1 gene.

The detail of the disclosure provided by Applicant, in view of the prior art, must encompass a wide knowledge, so that the Artisan of skill would be able to practice the invention as claimed by Applicant, without undue burden being imposed on such Artisan. This burden has not been met because it would require undue experimentation to discover any and all parameters and conditions and settings encompassed by the mediating, as claimed in claim 11 of the instant application. Additionally, it would require undue experimentation to determine an effective amount of a recombinant adeno-associated viral vector to be administered, and whether an AAV vector containing an HO-1 gene would be effective or any recombinant AAV vector, containing or not containing a particular exogenous gene would be effective in mediating expression of the HO-1 gene. Moreover, it would

require undue experimentation to test any and all host cells that may be amenable to producing rAAV/HO-1 *in vitro* and *in vivo*.

The Unpredictability Of The Art And The State Of The Prior Art

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The state of the prior art is effectively summarized by the references of Coffin et al. (U.S. Patent Application Publication 2005/0226847, filed Apr. 11, 2003) and Dzau et al. (U.S. Patent Application Publication 2003/0022870, filed June 3, 2002).

The art teaches the recombinant AAV vector expressing the HO-1 gene under the control of the CMV early promoter (column 2, p. 2, paragraph [0022]). The art also teaches that HO-1 encodes an enzyme that neutralizes the potent pro-oxidant activity of heme and that its multiple catalytic by-products bilirubin, carbon monoxide (CO) and free iron together exert powerful, pleiotropic effects, that include vasodilation, anti-inflammatory, anti-apoptotic and cytoprotective effects (paragraph [0063], column 1, p. 5). However, the art does not teach any and all effects on alterations of HO-1 gene expression, under any and all conditions that may be described as mediating. The art also fails to teach mediating of the expression of the HO-1 gene by any AAV vector, other than one containing the HO-1 gene. The prior art also fails to provide what may constitute as an effective amount of a recombinant adeno-associated viral vector to be administered. Coffin et al. teach producer host cells BHK and Vero, permissible for AAV production and HSV replication (paragraph [0080], column 1, page5), but do not provide for any and all host cells *in vitro* or *in vivo*.

Claim 9 of the instant application is drawn to a broad genus of host cells that may be utilized *in vitro* or *in vivo* and additionally constitute permissible hosts for the production of AAV and replication of HSV helper virus. The instant specification provides BHK host cells (line 5, p. 10, for example) for *in vitro* use, but does not describe any other host cells and further, fails to provide any guidance for *in vivo* production of rAAV/HO-1 virus. Therefore it would require undue experimentation by the skilled Artisan to carry out tests to discover all host cells permissible for rAAV/HO-1 virus production, and to determine whether said production may be carried out *in vivo*.

Claim 11 of the instant application is drawn to a broad genus of conditions and settings that could be involved in mediating expression, not apparent from the disclosure of the invention. Claim 11 also encompasses the administration of a recombinant AAV vector for gene therapy. The state of the prior art regarding gene therapy is effectively summarized by the references of Verma et al. (Nature 389:239-242; 1997) and Pfeifer et al. (Annual Review of Genomics and Human Genetics 2: 177-211; 2001), describing progress made in developing new vectors and also suggest vector targeting *in vivo* to be unpredictable and inefficient. Verma et al., reviews various vectors known in the art for use in gene therapy and problems associated with each implying that at the time of the claimed invention resolution to vector targeting had not been achieved in the art (entire articles). They highlight some advantages of using retroviral and adeno-associated viral vector in gene therapy but also acknowledge a greater level of skepticism in using these vectors in humans (Pfeifer et al., 2001; abstract). It is noted by the authors that more efficient and safe vectors are required to deliver genes to target cells for therapeutically effective levels of gene expression (Pfeifer et al., p 201).

It is further noted that, the specification does not teach how AAV viral vectors can be used effectively in administering transgene either via all possible routes of delivery. The specification also does not provide any guidance as to how studies in animal models can be extrapolated to human situations. In addition, prior art at the time of filing of this application as described *supra*, does not provide any convincing guidance in this regard either. The cited art clearly indicates an unpredictable status for the practice of gene therapy pertaining to the regulation of gene expression.

The instant specification provides rAAV mediated over-expression of HO-1 gene in grafts (lines 18-19, p.9) and AAV-mediated HO-1 expression (throughout the disclosure). The specification does not provide a description of what constitutes an effective amount of rAAV. The specification additionally fails to provide for any recombinant AAV vector (i.e. a virus not bearing the HO-1 gene), other than rAAV/HO-1 that can direct the expression of the HO-1 gene. Because mediating expression of the HO-1 gene (as claimed in claim 11), would comprise many different parameters, such as cell or tissue types or various titers of AAV, it would require undue experimentation by the skilled Artisan to carry out tests on all settings, conditions and concentrations of viral vector to determine all possible alterations in HO-1 gene activity levels, as claimed in claim 11.

In view of the lack of teachings or guidance provided by the specification with regard to any and all host cells and *in vivo* AAV production, and any and all effects on alterations of HO-1 gene

expression, under any and all conditions that may be described as mediating and the lack of teachings or guidance provided by the specification relating to an effective amount of rAAV, and for the specific reasons cited above, it would have required undue experimentation for an Artisan of skill to make and use the claimed invention. Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

The Amount Of Direction Or Guidance Presented And Working Examples

The specification fails to disclose adequate representations for different types of producer host cells, for *in vivo* virus production, and mediating of HO-1 expression. The specification discloses stable expression of HO-1 following delivery of 1×10^{12} vector genomes in syngeneic grafts (Example 1, p.13). However, the specification provides no additional examples of dose or viral titer. Moreover, Applicant's specification provides no examples of alterations in the level of expression of HO-1 gene or any effects on the expression of the HO-1 gene by recombinant AAV virus that does not contain the HO-1 gene. The specification is further devoid of any teachings of host cells other than BHK and does not describe AAV viral production in any settings other than *in vitro*. Moreover, the specification fails to provide teachings that enable the application of rAAV/HO-1 virus for gene therapy. The guidance provided by the specification amounts to an invitation for the skilled Artisan to try and follow the disclosed instructions to make and use the claimed invention. The specification merely discloses the expression of HO-1 gene following AAV gene transfer.

Quantity Of Experimentation

The quantity of experimentation in this area is extremely large, as there are a significant number of parameters, which would have to be studied and tested to make and definitively show that one is in possession of recombinant AAV virus production in a host cell *in vitro* or *in vivo* in any and all cell types; any and all effects on alterations of HO-1 gene expression, under any and all conditions that may be described as mediating, that can include gene therapy; and the administration of any recombinant AAV virus that can mediate expression of an HO-1 gene, including an AAV virus, not bearing the HO-1 gene. This would require a significant degree of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level Of Skill In The Art

The level of skill in the art at the time of invention is deemed to be high. However, because of the immaturity of the art, and its unpredictability, as shown by the other factors, one of skill in the art at the time of invention by Applicant would not have been able to make and/or use the invention claimed without undue experimentation.

Analysis And Summary

The guidance provided by the specification amounts to an invitation for the skilled Artisan to try and follow the disclosed instructions to make and use the claimed invention. The detail of the disclosure provided by Applicant, in view of the prior art, must encompass a wide knowledge, so that the Artisan of skill would be able to practice the invention as claimed by Applicant, without undue burden being imposed on such Artisan. In the instant case, and for the specific reasons cited above, in a highly unpredictable art where the identification and analysis of all parameters and conditions and settings encompassed by the mediating, and the determination of an effective amount of a recombinant adeno-associated viral vector to be administered and whether said mediating may be achieved by any recombinant AAV virus, the application of AAV/HO-1 virus for gene therapy, the discovery and evaluation of all permissible host cells and parameters for *in vivo* viral production, together with the large quantity of research required to define these unpredictable variables, and the lack of guidance provided in the specification, it is the position of the examiner that it would require undue experimentation for an Artisan of skill to make and use the claimed invention. Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-10 are rejected under 35 USC § 102(a) by Tsui, T-Y, Wu, X., Lau, C-K, Ho, D., Xu, T., Siu, Y-T, and Fan, S-T. (Circulation 107:2623-2629, 2003; of record). As stated on p.7, line 2 of the as filed specification, the current invention is published by Tsui et al. Tsui et al. teach the construction of the recombinant plasmid vector pSNAV/HO-1, comprising a heme oxygenase-1 (HO-1) gene (under Methods, column 1, p. 2624), together with their previous publication as an incorporated reference. Tsui et al. further teach the stable expression of HO-1 gene by rAAV-mediated gene transfer (under Results, second column, p. 2624). As there are no distinguishing features between the enabled invention of the instant claims (by Applicants Wu, X, and Tsui, T-Y), and the taught AAV vector cell strain BHK/HO-1, recombinant rAAV virus, and the large scale production of rAAV involving HSV1-rc, Tsui et al. anticipate all the limitations of claim 1-10.

Claims 1, 5-8 and 11 are rejected under 35 USC § 102(b) by Dzau et al. (U.S. Patent Application Publication 2003/0022870, filed Jun. 3, 2002). Claim 1 is directed to the recombinant plasmid vector pSNAV/HO-1, comprising an HO-1 gene. As stated in the specification, pSNAV1/HO-1 was constructed from pSV2Neo and PAV53 (page 9, lines 24-30 and Fig. 6), the components of which are readily available in the prior art and commonly used for vector construction. The only segment of pSNAV/HO-1 that is unique and relevant to the present invention is the AAV and HO-1 portion of the plasmid as depicted in Fig. 6. Figure 6 depicts HO-1 gene, operably linked to the CMV promoter, having a poly A signal at the 3' end and flanked by AAV ITR (AAV inverted terminal repeats) sequences. Dzau et al. teach recombinant AAV vectors expressing human heme oxygenase 1 (hHO-1) cDNA under the transcriptional control of the human cytomegalovirus (CMV) early gene promoter, rAAV/CMV-hHO-1, flanked by AAV inverted terminal repeats (ITR) and the BGH-pA providing the polyadenylation signal for the HO-1 gene (paragraph [0022], column 2, p. 2 and Fig. 1A). Therefore, each and every element of the AAV/HO-1 portion of the construct is present in Fig. 1A of the reference.

Claims 5-7 are product by process claims drawn to a recombinant virus. Dzau et al. teach the packaging, propagation and purification of recombinant AAV viral particles carrying the HO-1 gene

(paragraph [0084], column 1, p. 7). Claim 8 is drawn to recombinant virus rAAV/HO-1. Dzau et al. teach recombinant AAV virus carrying the HO-1 gene (paragraph [0084], column 1, p. 7 and paragraph [0100], p. 8). Following the packaging of said virus, the recombinant virus Dzau et al. is not distinguishable from the rAAV/HO-1 virus of claim 8. Therefore absent evidence to the contrary, Dzau et al. anticipate all the limitations of claims 5-8.

Claim 11 is drawn to a method of mediating expression of the HO-1 gene, wherein the method comprises administering an effective amount of a recombinant adeno-associated vector. When claim 11 is interpreted as an enabled method of increasing expression of the HO-1 gene, said administering encompassed by gene delivery to a particular cell or tissue, the claim is anticipated by Dzau et al. Dzau et al. teach rAAV, carrying the HO-1 gene, administered as " a vector for directed delivery of the cytoprotective gene HO-1 into the rat myocardium. A single delivery of an AAV/HO-1 composition was found to reduce myocardial injury". "AAV-mediated transfer of the hHO-1 gene led to a dramatic reduction (>75%) in left ventricular myocardial infarction" (paragraphs [0017 and 0018], column 1, p. 9).

Claims 2 and 3 are rejected under 35 USC § 102(a) by Coffin et al. (U.S. Patent Application Publication 2005/0226847, filed Apr. 11, 2003). Claim 2 is directed to AAV vector cell strain, said cell strain obtained by transforming a cell with pSNAV1/HO-1. Claim 2 is a product by process claim; as such, product by process claims are not limited to the manipulations of the recited steps, only the structure implied in the steps (MPEP 2113[R-1]). Therefore, claim 2 is drawn to any AAV vector cell strain. Claim 3 is directed to a BHK-21 AAV vector cell strain. The terms BHK and BHK-21 are used synonymously in the art to refer to the BHK cell line. Coffin et al. describe various AAV vector cell strains, including BHK, utilized for AAV virus production (Example 2, p. 7). Therefore, the AAV vector cell strain and the BHK-21 cell strain are anticipated by Coffin et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-10 are rejected under 35 USC 103(a) as being unpatentable over Coffin et al. (U.S. Patent Application Publication 2005/0226847, filed Apr. 11, 2003), in view of Dzau et al. (U.S. Patent Application Publication 2003/0022870, filed Jun. 3, 2002).

The claims 1-10 embrace a recombinant plasmid vector pSNAV/HO-1, comprising an HO-1 gene, said gene under the control of the CMV promoter and flanked by ITR sequences; an AAV cell strain BHK/HO-1; recombinant virus produced from said cell strain and a process for production of rAAV/HO-1 virus, comprising transfecting said cell strain with recombinant HSV virus.

Coffin et al. discuss the construction of an adeno-associated virus producer system, using a recombinant HSV virus (Abstract). The HSV virus of Coffin et al. serves as a helper virus for production of AAV, "having improved properties compared to previous herpes helper viruses" (paragraph [0006], column 1, p. 1). The HSV virus of Coffin et al. "comprises AAV rep and/or cap genes and/or AAV vector sequence" (paragraph [0017], column 2, p. 1), and may be used in an AAV producer line that supports the growth of the herpes virus. "A particularly preferred cell line is based on BHK or Vero cells" (paragraph [0080], column 1, p. 5).

At the time of the invention of the instant application, the prior art had demonstrated that AAV vectors might be used as vehicles for the delivery of genes of interest to various cells and tissues. Further, plasmid cloning vectors (for example pSV2neo), containing the neomycin resistance gene under the control of the SV40 promoter were routinely known and used in the art. While Coffin et. al. do not describe the use of the HO-1 gene in their AAV production and delivery system, Coffin et al. state: "An AAV vector of the invention may be formulated with a pharmaceutically acceptable carrier or diluent and/or may be administered to a patient in a method of treatment of a disease or disorder, for example by gene therapy", thus providing the motivation to include any therapeutically effective gene, including the HO-1 gene in the AAV vector and enable the efficient transfer of nucleic acid encoding HO-1 gene to cells or tissues of interest.

Dzau et al. describe methods of utilizing recombinant AAV vectors expressing human heme oxygenase 1 (hHO-1) cDNA under the transcriptional control of the human cytomegalovirus (CMV) early gene promoter, rAAV/CMV-hHO-1, having AAV inverted terminal repeats (ITR) encoding

replication and packaging signals and the BGH-pA providing the polyadenylation signal for the HO-1 gene (paragraph [0022], column 2, p. 2 and Fig. 1A). Dzau et al. further describe rAAV, carrying the HO-1 gene, administered as " a vector for directed delivery of the cytoprotective gene HO-1 into the rat myocardium. A single delivery of an AAV/HO-1 composition was found to reduce myocardial injury". "AAV-mediated transfer of the hHO-1 gene led to a dramatic reduction (>75%) in left ventricular myocardial infarction" (paragraphs [0017 and 0018], column 1, p. 9) "hHO-1 gene expression in left ventricle eight weeks after rAAV-mediated intramyocardial gene transfer" (paragraph [0024], column 2, p. 2 and Fig. 1C).

Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to utilize the combination of the AAV vector of Dzau et al. containing the HO-1 gene under the control of a CMV promoter sequence, in a process to produce recombinant AAV/HO-1 virus, using the recombinant HSV helper virus and BHK cell of Coffin, resulting in the practice of the instantly claimed invention. It would have been obvious to combine the AAV/HO-1 vector of Dzau et al. and the virus production system of Coffin et al., because the combination would result in improvements in virus packaging and virus production. The state of the art at the time of the invention had demonstrated the routine methods for construction of plasmid vectors containing selectable markers, containing AAV sequences. Therefore, an artisan of skill, having combined the elements of HSV helper virus containing the AAV rep and cap genes, the BHK cell line and an AAV vector capable of expressing the HO-1 gene, would have a reasonable expectation of success in producing rAAV/HO-1 virus in BHK cells.

Thus the claimed invention, as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

Claims 1-11, not allowable.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst William Phillips, whose telephone number is **(571) 272-0548**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is **(571) 272-3311**. The examiner can normally be reached Monday through Friday, between 7:00 am-4:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on **(571) 272-0731**. The fax phone number for the organization where this application or proceeding is assigned is **(571) 273-8300**. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

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